Peak Flow-Based Compared to Symptom-Based Written Action Plans

Question

Compared to a written action plan based on symptoms, does use of a written action plan based on peak flow monitoring improve outcomes?

Summary An[illegible] the[illegible]

Evidence neither supports nor refutes the benefits of written action plans based on peak flow monitoring compared to symptom-based plans in improving health care utilization, symptoms, or lung function. Just four studies, one including children, were available, and these studies had limitations (e.g., inadequate sample sizes and power to detect differences or potential bias in patient selection). The evidence does not clearly show that a peak flow-based action plan is better, but equivalent benefits have been demonstrated (Evidence B). Patient preferences and circumstances (e.g., inability to recognize or report signs and symptoms of worsening asthma) may warrant choosing peak flow monitoring.

The EPR-2 recommendations have not been changed. It is the opinion of the Expert Panel that peak flow monitoring for patients with moderate or severe persistent asthma should be considered because it may enhance clinician-patient communication and may increase patient and caregiver awareness of the disease status and control (Evidence B).

Rationale for the Question

The EPR-2 contains descriptions of the data available to assess asthma-related outcomes associated with peak flow monitoring. The EPR-2 Panel made clear that studies conducted at the time of EPR-2 were limited in number and quality and that findings were contradictory. Some guidance was available in the existing research related to patients with moderate or severe asthma who might benefit most from peak flow monitoring. It was considered useful to search the literature for additional, more recent studies.

Efforts to teach, encourage, and persuade patients to use a peak flow meter can be costly. Review of the question would help discern whether physician and patient time, energy, and money are warranted in terms of disease-related outcomes.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

The evidence review included studies that lasted at least 12 weeks and that compared the use of a peak flow meter-based plan plus medical management vs. a symptom-based action plan plus medical management, different schedules of peak flow monitoring, or the use of peak flow monitoring for routine chronic management vs. acute exacerbations. The comparison of peak flow monitoring to symptom monitoring was considered a strong approach, as there is widespread agreement among clinicians that patients should closely monitor their asthma symptoms. Peak flow monitoring values are thought to be beneficial objective measures that help patients determine the need to adjust their medicines and identify potentially urgent situations. Their use in patient self-management is thus dependent on an action plan provided by a clinician. Therefore, all studies included in the SRE compared peak flow monitoring-based written action plans with symptom-based written action plans.

Summary of Findings

Studies

Four studies met SRE inclusion criteria to assess the differences in outcomes when using a peak flow monitoring-based written action plan or a symptom-based action plan. (See the key evidence tables in this section). None of the studies met SRE criteria for high quality. In addition, the studies included in the review had significant limitations (e.g., all four studies had insufficient power to detect differences

between treatment and control groups). Further methodological weaknesses were noted in the question on written action plans, because three of the studies were included in both reviews (Cowie et al. 1997, Cote et al. 1997, and Charlton et al. 1990).

Results of Studies

Three of the four studies documented no significant differences on any outcome measure between peak flow monitoring-based plans and symptom-based plans. One study reported a difference in total emergency department visits in favor of the peak flow monitoring-based plan (Cowie et al. 1997). These findings are presented in the key evidence tables in this section. However, the significant methodologic weaknesses of the studies, as noted earlier, limit the conclusions. For example, the study reporting reduced emergency department visits did not compare change from baseline among groups, and the data suggest the effect may be attributable to a subset of patients who had very high frequency of emergency department visits.

In summary, the available evidence neither supports nor refutes the use of peak flow monitoring-based action plans vs. symptom-based plans in improving outcomes.

Recommendations for EPR Update

Current EPR-2 recommendations should not be changed until there is clear evidence that one monitoring method is superior to another. The Expert Panel recommends the following blue text be incorporated into EPR-2.

Component 1: Measures of Assessment and Monitoring; Peak Flow Monitoring
(pages 28 through 33 in EPR-2)

Peak flow monitoring can be used for short-term monitoring, managing exacerbation, and daily long-term monitoring. When used in these ways, the patient's measured personal best is the most appropriate reference value. Thus far, the few studies that have isolated a comparison of peak flow and symptom monitoring have not been sufficient to assess the relative contributions of each to asthma management. The literature does suggest which patients may benefit most from peak flow monitoring. (See box 1, Peak Flow Monitoring Literature Review.)

A systematic review of the evidence conducted in 2002 concluded that evidence at this time does not clearly show that a peak flow monitoring-based action plan is better than a symptom monitoring-based plan in improving outcomes, but it does show similar benefits (SRE-Evidence B). In the opinion of the Expert Panel, there are two distinct arguments for keeping the recommendations to consider peak flow monitoring for patients with moderate or severe persistent asthma: (1) peak flow monitoring appears to provide a way to enhance clinician-patient communication and (2) either peak flow or symptom self-monitoring appears to increase patient awareness of asthma status and control, thereby helping patients attribute symptoms to their disease.

If this is the case, either method, if taught and [illegible] correctly, may be equally effective (Evidence B). Preferences for objective measures in patient circumstances, such as inability to perceive or report signs and symptoms of worsening asthma, warrant the use of peak flow monitoring. The Expert Panel believes that the associated patient time, energy, and costs are, therefore, justified [illegible]. This does not, however, change the recommendation that all patients with persistent asthma have a peak flow meter and know how to use it.

The Expert Panel concludes, on the basis of this literature and the Panel's opinion, that:

- Patients with moderate or severe persistent asthma should learn how to monitor their PEF and have a peak flow meter at home.
- Peak flow monitoring during exacerbations of asthma is recommended for patients with moderate or severe persistent asthma to:
  - Determine severity of the exacerbation.
  - Guide therapeutic decisions (see component 3, Managing Exacerbations, and figure 4–5) in the home, clinician's office, or emergency department.

- Long-term daily peak flow monitoring is helpful in managing patients with moderate or severe persistent asthma to:
  - Detect early changes in disease status that require treatment.
  - Evaluate responses to changes in therapy.
  - Provide assessment of severity for patients with poor perception of air flow obstruction.
  - Afford a quantitative measure of impairment.
- If long-term daily peak flow monitoring is not used, a short-term (2- to 3-week) period of peak flow monitoring is recommended to:
  - Evaluate responses to changes in chronic maintenance therapy.
  - Identify temporal relationship between changes in PEF and exposure to environmental or occupational irritants or allergens. It may be necessary to record PEF 4 or more times a day (Chan-Yeung 1995).
  - Establish the individual patient's personal best PEF.
- The Expert Panel does not recommend long-term daily peak flow monitoring for patients with mild intermittent or mild persistent asthma unless the patient, family, and/or clinician find it useful in guiding therapeutic decisions. Any patient who develops severe exacerbations may benefit from peak flow monitoring (Evidence B).

Limitations of long-term peak flow monitoring include:

- Difficulty in maintaining adherence to monitoring (Reeder et al. 1990; Chmelik and Doughty 1994; Malo et al. 1993), often due to inconvenience, lack of required level of motivation, or lack of a specific treatment plan based on PEF.
- Potential for incorrect readings related to poor technique, misinterpretation, or device failure.

Whether peak flow monitoring, symptom monitoring, or a combination of approaches is used, the Expert Panel believes that self-monitoring is important to the effective self-management of asthma. The nature and intensity of self-monitoring should be individualized, based on such factors as asthma severity, patient's ability to perceive or report airflow obstruction, availability of peak flow meters, and patient preferences.

Recommendations for Future Research

The utility of peak flow monitoring and the circumstances where it is beneficial continue to be salient issues in asthma self-management. The following questions for research deserve attention:

- Does peak flow monitoring provide benefits over symptom monitoring? Studies of adequate power are needed to settle the question.
- Which patients (e.g., those with more severe disease, of different ages, or with special circumstances or preferred language or literacy concerns) are most likely to benefit from peak flow monitoring? Studies in children are especially needed because children may not report symptoms as easily or readily as adults.
- What type of benefits can be accrued from peak flow monitoring?
  - Identification of precipitants to symptoms?
  - More timely adjustment of medicines?
  - Improved perception of airflow obstruction?
- Is peak flow monitoring more likely to be used by patients regularly instead of only during exacerbations? Short term vs. long term? What are the relative benefits of short term use in producing disease-related outcomes?

The SRE stimulates questions that go beyond those related to written action plans and peak flow vs. symptom monitoring. Answers to the following related and important research questions may enhance efforts to educate patients and foster self-management:

- Which components of self-management interventions are most powerful (i.e., account for the greatest variance in disease-related outcomes)?

- What is the minimum core of information and skills required in self-management interventions to produce desired outcomes?
- Which types of interventions (and which of their components) are most effective given the patient's disease severity?
- Which members of the health care team or education partners (e.g., teachers and social workers) best provide which components of self-management education?
- What new venues (e.g., worksites, community centers, churches) might provide greater access to patients who are members of underserved populations?

Key Evidence Tables

Table 2-4. Study Characteristics

Citation	Study D[illegible]	Study Setting	Eligibility	Comments
PFM-based acti[illegible]	[illegible]	[illegible] action plan		
Cowie, Revitt, Underwood et al. 1997	Randomized; parallel, controlled	Country: Canada Funding: Foothills Hospital, Calgary Tx Setting: Primary/specialty combination, university Multicenter	Patient eligibility based on symptoms and utilization. Inclusions: Treatment for an exacerbation of asthma in an ER or attending a university asthma clinic; history of receiving urgent treatment for asthma in the previous 12 months	Subjects were recruited by contacting those who had been treated for an exacerbation of asthma in an emergency department or those attending a university asthma clinic with a history of having received urgent treatment for their asthma in the previous 12 months.
Cote, Cartier, Robichaud et al. 1997	Randomized; parallel, controlled	Country: Canada Funding: Pharm. Ind., grant Tx Setting: Specialty care, nonuniversity Multicenter	Patient eligibility based on lung function and symptoms. FEV_1 Postbronchodilator 85–100% of predicted; PEF minimum 85% of predicted; PEF variability minimum 0%; Methacholine Exclusion: Previous enrollment in an asthma educational program	In discussion "although the control group received more than the usual care treatment, none received book, none had written action plan, none had structured education or PFM at home after run-in"; run-in = 2–6 weeks; diagnosis of asthma included need to take daily anti-inflammatory agents; were excluded.
Turner, Taylor, Bennett et al. 1998	Randomized; parallel, controlled	Country: Canada Funding: Pharm. Ind. + other, not specified Tx Setting: Primary care, nonuniversity	Patient eligibility based on lung function and symptoms. Inclusions: Methacholine PC20 maximum 7.9; using inhaled corticosteroids Exclusions: Previous PFM use; significant comorbid conditions	Patients were randomized after stratification for severity of airway responsiveness using values of PC20 methacholine <2 mg/mL or >2 mg/mL. 150 screened, 117 enrolled.
Charlton, Charlton, Broomfield et al. 1990	Randomized; parallel, controlled	Country: United Kingdom Funding: Clare Wand Fund, Scientific Foundation of RCP Vitalogap Tx Setting: Specialty care, nonuniversity	Patient eligibility based on symptoms only. Inclusion: Patients on repeat prescribing register	Patients were not randomly selected for participation. Letters were sent to patients on the repeat prescribing register, and invited them to make an appointment with a nurse.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 2-5. Lung Function Outcomes: FEV_1

Citation	Study Arm	Number Enrolled	Number Evaluable	Treatment Duration (weeks)	
Peak flow meter (PFM)-based action plan vs. symptom-based action plan					
Turner, Taylor, Bennett et al. 1998	Symptom-based action plan	48	48	24	
	PFM-based action plan	44	44	24	
Charlton, Charlton, Broomfield et al. 1990	Symptom-based action plan				
	PFM-based action plan				
Cowie, Revitt, Underwood et al. 1997	Symptom-based action plan	45			
	PFM-based action plan	46			
Cote, Cartier, Robichaud et al. 1997	Symptom-based action plan	45			
	PFM-based action plan	50			

Table 2-6. Symptom Score Outcomes

Citation	Study Arm	Number Enrolled	Number Evaluable	Treatment Duration (weeks)	
Peak flow meter (PFM)-based action plan vs. symptom-based action plan					
Turner, Taylor, Bennett et al. 1998	Symptom-based action plan	48	48	24	
	PFM-based action plan	44	44	24	
Charlton, Charlton, Broomfield et al. 1990	Symptom-based action plan				
	PFM-based action plan				
Cowie, Revitt, Underwood et al. 1997	Symptom-based action plan	45	45	24	
	PFM-based action plan	46	46	24	
Cote, Cartier, Robichaud et al. 1997	Symptom-based action plan	45			
	PFM-based action plan	50			

	Baseline FEV_1*	Final FEV_1	P-Value	P-Value Comparison	Comments
	78.7 +/- 18.9% of predicted	86.1 (mean) % of predicted			FEV_1 in L, mean (SD) was 2.86 (0.88).
	78.1 +/- 19.7% of predicted	83 (mean) % of predicted	NS	Absolute value, Tx vs. Ctl	FEV_1 in L, mean (SD) was 2.84 (0.86).
	79 +/- 18% of predicted				Number of subjects with <60% predicted was 8.
	82 +/- 20.5% of predicted				Number of subjects with <60% predicted was 9.

* FEV_1 pre- or postbronchodilator status unknown unless otherwise indicated.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

	Baseline Daytime Symptom Score	Final Daytime Symptom Score	P-Value	Final Nighttime Symptom Score	P-Value	Comments
	9.1 (mean; scale, 0–24)	5.2 (mean; scale, 0–24)				Not sure if reported score is actually a mean; daytime score is really overall score where 24 is max and higher value = more asthma symptoms.
	8.2 (mean; scale, 0–24)	3.2 (mean; scale, 0–24)	NS[1]			Not sure if reported score is actually a mean; daytime score is really overall score where 24 is max and higher value = more asthma symptoms.

[1] Treatment comparison-absolute value, Tx vs. Ctl
[2] Treatment comparison not specified

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Chan-Yeung M. Assessment of asthma in the workplace. American College of Chest Physicians Consensus Statement. Chest 1995;108(4):1084–117.

Charlton I, Charlton G, Broomfield J, Mullee, MA. Evaluation of peak flow and symptoms only self management plans for control of asthma in general practice. BMJ 1990;301(6765):1355–9.

Cote J, Cartier A, Robichaud P, Boutin H, Malo JL, Rouleau M, Fillion A, Lavallee M, Krusky M, Boulet LP. Influence on asthma morbidity of asthma education programs based on self-management plans following treatment optimization. Am J Respir Crit Care Med 1997;155(5):1509–14.

Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. Chest 1997;112(6):1534–8.

Turner MO, Taylor D, Bennett R, Fitzgerald JM. A randomized trial comparing peak expiratory flow and symptom self-management plans for patients with asthma attending a primary care clinic. Am J Respir Crit Care Med 1998;157(2):540–6.

Asthma
for Clinical Reference
EPR-3
Expert Panel Report
Guidelines for the
Diagnosis and
Management of
Asthma
3 Prevention

In deciding when to initiate daily therapy for patients with asthma, clinicians consider the goals of controlling and preventing symptoms, as well as the possibility of preventing further progression of the underlying disease. This section of the EPR—Update 2002 addresses the question of whether early initiation of daily inhaled corticosteroid treatment is warranted to prevent progression of asthma.

Effect of Treatment on Progression of Asthma

Question

For patients with mild or moderate persistent asthma, does early intervention of long-term-control therapy (i.e., inhaled corticosteroids) prevent progression of asthma as indicated by changes in lung function or severity of symptoms?

Summary Answer to the Question

Evidence regarding the benefits of early treatment of asthma in preventing the progression of disease is insufficient to draw conclusions. But available evidence does not support the assumption that children 5 to 12 years of age with mild or moderate persistent asthma experience a progressive decline in lung function (SRE-Evidence A). Further, the evidence indicates that although inhaled corticosteroids provide superior control and prevention of asthma symptoms during treatment of childhood asthma, symptoms and airway hyperresponsiveness worsen when treatment is withdrawn (SRE-Evidence A). This evidence suggests that the therapy controls but does not modify the disease in this age group. Studies in children younger than 3 years of age and in adults document declines in lung function. Studies of whether treatment can prevent these declines in lung function or symptom severity have not yet been conducted in young children and are inconclusive in adults. Revisions to the EPR-2 are recommended to reflect the new understanding of the progression of asthma.

Rationale for the Question

A common question confronting clinicians and patients is: At what point in the disease process—as reflected by the level of clinical signs and symptoms as well the duration of disease—should daily long-term-control therapy be initiated? Although the effectiveness of inhaled corticosteroids in controlling and preventing symptoms of asthma and improving pulmonary function is well documented, an important question is whether inhaled corticosteroids modify the natural history of the disease. If the progression of asthma is from airway inflammation to airway remodeling and some irreversible airway obstruction, then anti-inflammatory medication (i.e., inhaled corticosteroids) given early in the course of disease may interrupt this process and prevent permanent declines in lung function. In order for early initiation of inhaled corticosteroids to be more beneficial than delayed initiation, two assumptions must be valid: as a group, people with mild or moderate persistent asthma experience a progressive decline in lung function that is measurable and clinically significant, and treatment with inhaled corticosteroids prevents or slows this decline, in addition to controlling asthma symptoms. A SRE was conducted to evaluate the current literature on the effect of intervention of inhaled corticosteroids in altering the progression of disease.

Background Information

Addressing the question about the effect of inhaled corticosteroids on the progression of disease requires answering a series of questions: What is the progression of asthma? Does intervention alter the progression? When is the appropriate time to intervene? The Expert Panel's review of the literature on the progression of asthma is presented here as a context for interpreting the studies evaluated in the SRE.

I Natural History of Persistent Asthma

Children

It has been well established that asthma is a variable disease: It can vary among individuals, and its progression and symptoms can vary within an individual's experience over time. It has been postulated that the persistence or increase of asthma symptoms over time is accompanied by a progressive decline in lung function. Recent research suggests that this may not be the case; rather, the course of asthma may vary markedly between young children, older children and adolescents, and adults, and this variation is probably more dependent upon age than symptoms.

A prospective cohort study in which followup began at birth revealed that in children whose asthma-like symptoms began before 3 years of age, deficits in lung growth associated with the asthma occurred by 6 years of age (Martinez et al. 1995). Continued followup on lung function measures taken at 11 to 16 years of age found that compared to the group of children who experienced no asthma symptoms for the first 6 years of life, the group of children whose asthma symptoms began before 3 years of age experienced significant deficits in lung function at 11 to 16 years of age, but the group whose asthma symptoms began after 3 years of age did not experience deficits in lung function.

A longitudinal study of children 8 to 10 years of age found that bronchial hyperresponsiveness was associated with declines in lung function growth in both children with active symptoms of asthma and children without (Xuan et al. 2000). Thus, symptoms neither predicted nor determined lung function deficits in this age group.

Baseline data from the Childhood Asthma Management Program (CAMP) study support the finding that the individual's age at the time of asthma onset influences declines in lung function growth. At the time of enrollment of children with mild or moderate persistent asthma at 5 to 12 years of age, an inverse association between lung function and duration of asthma was noted (Zeiger et al. 1999). Although the analysis did not distinguish between age of onset and duration of asthma, it can be inferred that because the average duration of asthma was 5 years and the average age of the children was 9 years, most children with the longer duration of asthma started experiencing symptoms before 3 years of age. The data suggest that these were the children with lowest lung function levels. After 4 to 6 years of followup, the children in the CAMP study, on average, did not experience deficits in lung growth (as defined by postbronchodilator FEV_1), regardless of their symptom levels or treatment they received (CAMP 2000).

These results suggest that most of the deficits in lung function growth observed in childhood asthma occur in children whose symptoms begin during the first 3 years of life, and the onset of symptoms after 3 years of age usually is not associated with significant deficits in lung function growth. Further, at least for children with mild or moderate persistent asthma, there do not appear to be deficits in lung function growth from 5 to 17 years of age.

Thus, the most promising target for interventions designed to prevent deficits in lung function and perhaps the development of more severe symptoms later in life would be those children who have symptoms before 3 years of age and are destined to develop persistent asthma. However, it is important to distinguish this group from the majority of children who wheeze before 3 years of age and do not experience any more symptoms after 6 years of age (Martinez et al. 1995). Until recently, no validated algorithms were available to predict which children among those with asthma-like symptoms early in life would go on to have persistent asthma. Data obtained from long-term longitudinal studies of children enrolled at birth generated such a predictive index. This predictive index identified the following risk factors for developing persistent asthma

symptoms among children younger than 3 years of age who had more than three episodes of wheezing during the previous year: either physician diagnosis of atopic dermatitis/eczema or a parental history of asthma or two out of three of the following asthma-associated phenotypes—peripheral blood eosinophilia, wheezing apart from colds, or physician-diagnosed allergic rhinitis. When the index was applied to a birth cohort that was followed through 13 years of age, 76 percent of the children who were diagnosed with asthma after 6 years of age had a positive predictive index; moreover, 97 percent of the children in this cohort who did not have asthma after 6 years of age had a negative asthma predictive index before 3 years of age (Castro-Rodriguez et al. 2000).

Adults

Accelerated loss of lung function appears to occur in adults with asthma. In a study of adults with asthma who received 2 weeks of high-dose prednisone if airflow obstruction persisted after 2 weeks of bronchodilator therapy, the degree of persistent airflow obstruction correlated with both the severity and the duration of their asthma (Finucane et al. 1985).

Two large prospective epidemiological studies evaluated the rate of decline in pulmonary function in adults with asthma. In an 18-year prospective study of 66 nonsmokers with asthma, 26 smokers with asthma, and 186 control participants with no asthma, spirometry was performed at 3-year intervals (Peat et al. 1987). Seventy-three percent of the study group underwent at least 6 spirometric evaluations. The slope for decline in lung function (FEV_1) was approximately 40 percent greater for the participants with asthma than for those with no asthma. This did not appear to be the result of extreme measurement produced by a few participants, because fewer than 25 percent of the participants who had asthma were measured with a slope less steep than the mean for those who did not have asthma. In another study, three spirometry evaluations were performed in 13,689 adults (778 who had asthma, 12,911 who did not have asthma) over a 15-year period (Lange et al. 1998). The average decline in FEV_1 was significantly greater in those who had asthma (38 mL per year) than those who did not have asthma (22 mL per year). Although, in this study, asthma was defined simply by patient report, the researchers noted that because the 6 percent prevalence rate for asthma did not increase in this cohort as they increased in age, it is likely that the subjects who reported having asthma did indeed have asthma rather than chronic obstructive pulmonary disease (COPD). It is not possible to determine from these studies whether the loss of pulmonary function occurred in those who had mild or moderate asthma or only in those who had severe asthma. Nevertheless, the data support the likelihood of potential accelerated loss of pulmonary function in adults who have asthma.

Taken together, these longitudinal epidemiological studies and clinical trials indicate that the progression of asthma, measured by declines in lung function, varies in different age groups. Declines in lung function growth observed in children appear to occur by 6 years of age and occur predominantly in those children whose asthma symptoms started before 3 years of age; children 5 to 12 years of age with mild or moderate persistent asthma do not appear to experience declines in lung function through 11 to 17 years of age. There is also evidence of progressively declining lung function in adults.

Data on the effect of interventions to influence the progression of asthma, measured by declines in lung function, airway hyperresponsiveness, or the severity of symptoms, were evaluated in the SRE.

Systematic Review Evidence

Methods of Literature Search

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the criteria for selecting studies for this question were as follows:

- Some or all patients started long-term-control medication (inhaled corticosteroids, leukotriene modifiers, cromolyn, nedocromil, or theophylline) during the study

AND

- The treatment group was treated immediately following diagnosis of asthma compared to a control group that received the same treatment after a delay

OR

- The population was stratified by the duration of asthma prior to the initiation of long-term-control medication and outcomes compared across the different strata.

- Treatment duration was at least 1 year.

- At the start of the study, no more than 10 percent of the population was currently being treated with or had been continuously (more than 1 month) treated in the past with the long-term-control medication being studied.

Summary of Findings

Studies

Although the objective was to review the literature on the effects of any long-term-control medications (e.g., inhaled corticosteroids, leukotriene modifiers, cromolyn, nedocromil, theophylline), the available studies were limited to research on inhaled corticosteroids. (See the key evidence tables in this section for a summary description of the eligible studies.)

Four studies reporting on a total of 475 asthma patients met the inclusion criteria for this key question: two randomized controlled trials (RCTs) (Haahtela et al. 1994; Overbeek et al. 1996) and two single-arm studies (Selroos et al. 1995; Agertoft and Pedersen 1994). Just one of the studies enrolled children who were 3 to 11 years of age (Agertoft and Pedersen 1994). According to EPR-2 classification of severity, two studies involved mild asthma (baseline FEV_1 greater than 80 percent predicted) (Haahtela et al. 1994; Agertoft and Pedersen 1994), and two involved moderate asthma (Overbeek et al. 1996; Selroos et al. 1995). Each of the two RCTs (Haahtela et al. 1994; Overbeek et al. 1996) was an open-label extension of an RCT originally intended to evaluate the efficacy of inhaled corticosteroids. In these studies, the patients who were initially assigned to the noncorticosteroid-treated control group were subsequently administered inhaled corticosteroids at the conclusion of the original RCT. Each of the single-arm studies (Selroos et al. 1995; Agertoft and Pederson 1994) analyzed a cohort of patients treated in a hospital-based clinic, where the patients were stratified by the individual's duration of asthma prior to initiating inhaled corticosteroids treatment, and outcomes were compared across the strata.

The duration of the followup was 3 years in the randomized trials and 2 and 3.7 years, respectively, in the single-arm studies. Haahtela et al. (1994) treated one group with inhaled corticosteroids for 24 months, then treated the delayed inhaled corticosteroid group for 12 months. Overbeek et al. (1996) treated one group with inhaled corticosteroids for 30 months, initiated treatment with inhaled corticosteroids in the delayed group, and followed both groups for an additional 6 months. In the single-arm studies, patients starting on inhaled corticosteroids were followed for 2 years in one study (Selroos et al. 1995) and for 2 to 6 years (mean: 3.7 years) in the final study (Agertoft and Pedersen 1994).

All four trials reported lung function outcomes, but no two studies used the same measure to report change in lung function from baseline. Neither of the two RCTs (Haahtela et al.; Overbeek et al. 1996) met the SRE criteria that define higher quality studies. Neither study maintained blinding to treatment throughout the course of the study. For both, the rate of dropouts/withdrawals exceeded the established threshold. Analyses were not done by intent to treat or in a manner to minimize dropout bias. With respect to SRE asthma-specific indicators of study quality, both randomized trials established reversibility on lung function measurements and controlled for use of other asthma medications, but neither study reported power calculations for outcomes, adequately accounted for excluded patients, specified a priori which were primary outcomes for analysis, reported compliance, or controlled for the effects of seasonality on outcomes.

A major limitation of the single-arm studies is that patients entered the study at varying time points in the duration of their disease, making it impossible to compare outcome data at a uniform time point. A second limitation in such studies is the high

potential for selection bias. It is likely that patients who have had asthma longer will have more severe disease, both because of disease progression and because asthma is more likely to remit in milder cases.

Finally, the SRE literature search found no prospective studies to address this key question in the specific population of interest. As a result, the available evidence from studies that compared early with delayed inhaled corticosteroid treatment has notable limitations with respect to the study population, time frames for study entry and followup, clarity of reporting with respect to details of interest to the question, and the use of appropriate control groups. For some trials, it was impossible to accurately calculate the number of enrolled or evaluable patients of interest, because reporting of one or the other number was combined with other patient groups (e.g., patients who have COPD or individuals with severe asthma).

The SRE also included consideration of results from CAMP 2000, although the research was not published until after the SRE literature search, and the study design does not address the question of intervention timing (early vs. delayed treatment). The study is considered in the SRE because it evaluates the long-term (4 to 6 years) effect of treatment on lung growth and asthma symptoms in more than 1,000 children with mild or moderate asthma. The RCT comparing inhaled corticosteroids and nedocromil with placebo (all groups received as-needed $beta_2$-agonists) met SRE criteria for high quality. Thus, the study provides robust evidence on the course of childhood asthma.

Results of Studies

Of the four studies identified by the SRE literature search, the randomized trial by Haahtela, although small (52 evaluable study participants), is the most relevant in terms of study design and population. The design includes comparisons that directly address the key question of interest, and the population is limited to individuals with mild asthma who were enrolled in the study at a similar point in the history of their disease—i.e., a diagnosis within the 12 months prior to enrollment. The first phase of the study was a randomized control comparison of a group treated daily with inhaled corticosteroids and a group treated with daily $beta_2$-agonists, and followed for 24 months. The second phase of the study was an open-label study in which 67 percent of the original $beta_2$-agonist treatment group was given inhaled corticosteroids and followed for 12 more months; the original inhaled corticosteroid treatment group was either continued on a reduced dose of steroid or given a placebo. Outcomes at the end of 3 years indicated improvements in lung function measures and symptom scores in both groups, with larger increases occurring in the immediate inhaled corticosteroid group compared to the delayed inhaled corticosteroid group (FEV_1 0.15 L vs. 0.02 L; PEF 42 L/min vs. 15 L/min; PC15 5.0 vs. 4.22 DD histamine; symptom score change of 0.8 vs. 0.4 from a mean baseline of 2.2 on a 1 to 10 point scale). Although these findings appear to support the hypotheses that an irreversible decline in lung function can occur in asthma not treated with an anti-inflammatory medication and that treatment with inhaled corticosteroids may have an impact on decline, methodologic features of the study limit the conclusions that can be reached. No statistical tests of significance were performed comparing baseline and 3-year outcomes between the immediate and the delayed treatment groups, and the differences are of unknown clinical significance because the magnitude is of a size that could be explained by bias. Bias may have occurred due to the lack of strict comparability between the double-blind and open-label phases of the trial, lack of controls for doses of inhaled corticosteroids, and a high rate of withdrawal from the study during the open-label phase (36 of 53 patients in the delayed treatment group and 16 of 50 in the immediate treatment group were available for analysis at 3 years), with no tests of comparability between withdrawals and continuing patients.

The second randomized trial identified in the SRE is also an open-label extension of a double-blind RCT designed to evaluate the efficacy of inhaled corticosteroids. The study had three treatment groups: one received inhaled corticosteroids, a second received inhaled ipratropium, and a third received placebo, but all groups received an inhaled $beta_2$-agonist four times a day (Overbeek et al. 1996). After 30 months of treatment, the asthma patients in the groups not receiving inhaled corticosteroids were given that agent and followed 6 additional

months in an open-label observation. This allows comparison of a group (49 patients) receiving immediate vs. a group (53 patients) receiving delayed inhaled corticosteroids for asthma. Results reported a greater but not statistically significant rise in FEV_1 during the initial 3 months of inhaled corticosteroid therapy for the immediate treatment group (13.8 percent increase vs. 8.5 percent increase; $p = 0.13$), and a statistically significant rise in PC15 values for the initial 6 months of inhaled corticosteroids in the immediate treatment group (1.77 doubling dose vs. 0.79, $p = 0.03$), and no differences in symptom score values. The study suggests the possibility of some benefit for immediate treatment, but conclusions are severely limited by several methodologic problems. For example, it is not clear at what point in the individual patient's disease process the treatment was started; the study populations include a mix of patients with severe asthma and COPD, and there were no comparisons made relevant to the key question—i.e., comparison of baseline and final lung function measured at the end of the trial. Further, there was a high dropout rate (less than half the eligible patients participated in the extended open-label phase) with no analysis of the withdrawals, which may introduce bias.

For the single-arm studies, one study enrolled 105 consecutive patients started on inhaled corticosteroids and observed them for 2 years (Selroos 1995). Changes in lung function outcomes (FEV_1 percent predicted and PEF percent predicted) were compared among the patients, according to groups stratified by duration of asthma at the onset of treatment (0 to 6 months, 14 patients; 6 to 12 months, 35 patients; 12 to 14 months, 13 patients; 24 to 60 months, 19 patients; 60 to 120 months, 15 patients). All strata were compared to the 0- to 6-month duration group; no comparison among strata was reported. The greatest increase in lung function measures occurred in the group with the shortest (0 to 6 months) duration of asthma (17 percent increase in FEV_1 percent predicted); and the least increase occurred in the group with the longest (60 to 120 months) duration of asthma (0 percent increase, $p < 0.01$). All other strata except the 24- to 60-month group had significantly less degree of lung function improvement than the 0- to 6-month group, but of varying magnitude.

For PEF, the 0- to 6-month group had a 21 percent increase in percent predicted values, compared with a 2 percent increase in the 60- to 120-month group ($p < 0.05$), but differences among the other strata varied in magnitude and significance. Although the stratification accounted for differences in duration of disease, it is impossible to compare outcome data at a uniform time point in the disease. Further, baseline differences in lung function and asthma severity indicate some selection bias. Finally, approximately one-third of the study participants were current or exsmokers, and the proportion of current smokers varied from 0 percent to 29 percent in the different groups. Thus, study design features, variance in final outcome measures among the strata, and the confounding factors of asthma severity and smoking limit interpretation of the results.

The second single-arm study identified by the SRE is a nonrandomized, prospective controlled trial of long-term outcomes in 216 children treated with inhaled corticosteroids for a mean of 3.7 years compared to 62 children who declined recommendations for inhaled corticosteroid treatment (Agertoft and Pedersen, 1994). In a supplemental cohort analysis, patients in the inhaled corticosteroid group were stratified by prior duration of asthma (0 to 2 years, 2 to 3 years, 3 to 5 years, and more than 5 years). This allowed a comparison relevant to the key SRE question. The main reported outcome was annual change in percent predicted FEV_1, calculated by linear regression. Results showed a mean change in FEV_1 per year of 8.2 percent for the 0- to-2-year group, 6.7 percent for the 2- to 3-year group, 3 percent for the 3- to 5-year group, and 2.4 percent for the more than 5-year group. A statistically significant correlation existed between the duration of asthma and the estimated change in FEV_1 per year; however, the differences were not significant between every group (e.g., the less than 2 vs. the 2- to 3-year strata or the 3- to 5-year vs. the more than 5-year strata). A major difficulty in interpreting these results is that the linear regression assumes a linear change in outcomes over the entire course of the study. However, it is well documented in the literature that there is a pattern of a sharp initial rise in FEV_1 during the first 3 months of inhaled corticosteroid treatment that is then followed by a plateau. Indeed, the final difference in FEV_1 percent predicted between the less than 2-year strata

(101 percent) and the more than 5-year strata (96.2 percent) was 4.8 percent after a mean of 3.7 years of treatment. This is considerably less than the 5.8 percent per year difference estimated by the linear regression model applied to the data.

The results of the CAMP 2000 study influence the conclusions derived from the SRE (CAMP 2000). This study is a three-arm, RCT evaluating the outcome effects of inhaled corticosteroids or nedocromil sodium compared to placebo in 1,041 children over a mean followup period of 4.3 years. The primary outcome measure was postbronchodilator FEV_1. Although the design of CAMP does not address the question of early versus delayed intervention (the average duration of asthma was 5 years for the study population), it does address the question of the effect of intervention with two treatments on disease progression as defined by loss in FEV_1 percent predicted.

CAMP researchers found an initial, highly statistically significant difference between treatment and control groups for change in postbronchodilator FEV_1 in the first year of the study, but no difference in change from baseline to the end of the 4- to 6-year followup period. This outcome measure was chosen to minimize the effects of reversible airway constriction and individual variability over time that are observed with prebronchodilator FEV_1. The finding of no difference in postbronchodilator FEV_1 and minimal change overall in lung function over 4 to 6 years for the entire study population does not support the hypothesis that treatment with inhaled corticosteroids improves lung growth in children with mild or moderate persistent asthma. It is of particular interest that CAMP does not document progressive decline in lung function in the placebo group, or significant improvement from baseline in the treatment groups (CAMP 2000). Similar to the findings related to lung function outcomes, no progressive decline in symptoms with the placebo groups was noted. Symptom scores and night-awakening scores improved over the course of the study in both the inhaled corticosteroid and placebo groups, with greater improvement throughout the study period shown in the inhaled corticosteroid group. The improvements in the placebo group may have been a result of the close medical supervision and patient education given to all study participants, but the greater improvements in symptom scores and airway hyperresponsiveness indicate superior effectiveness of inhaled corticosteroid treatment. However, after inhaled corticosteroid treatment was withdrawn, symptom scores and airway hyperresponsiveness values were no different between groups. This finding indicates that the inhaled corticosteroids provided superior control and prevention of symptoms, but did not modify underlying disease. The finding that the placebo group did not experience a decline in lung function does not support the assumption of such a decline in children with mild or moderate asthma in this age group.

As noted in the Background Information section, it is likely that a progressive decline in lung function occurs in younger children and in adults. It is also possible it occurs in individuals with more severe asthma.

The studies identified by the SRE most relevant to addressing the question of whether early intervention with inhaled corticosteroids can prevent progression of disease were suggestive of benefit, but methodologic issues severely limit the conclusions that may be drawn. Additional consideration of the CAMP study supports cautious interpretation of the studies identified in the SRE. Although none of these studies was designed specifically to compare immediate versus delayed treatment in preventing progression of disease, the results provide critical insights for future research. At this time, the Expert Panel concludes that the evidence is insufficient to permit conclusions regarding the use of early intervention vs. long-term-control medication to prevent progression of disease.

Recommendations for EPR Update

Modifications in the EPR-2 are necessary to reflect the current understanding of natural history of persistent asthma, based on the SRE and review of additional, recently published studies that provide insights on the progression of asthma. It is clear that further research is needed to define the benefits of early intervention, the appropriate time of intervention, the nature of asthma as a progressive disease, and the effect of medications on preventing

progression. Until this information is available, the Expert Panel recommends the following revisions to EPR-2 (the blue text indicates new text), based on the SRE.

Introduction: Pharmacologic Therapy (page 4, column 2, final paragraph in EPR-2)

Observations into the basic mechanisms of asthma have had a tremendous influence on therapy. Because inflammation is considered an early and persistent component of asthma, therapy for persistent asthma must be directed toward long-term suppression of the inflammation. Thus, EPR-2 continues to emphasize that the most effective medications for long-term-control are those shown to have anti-inflammatory effects. For example, early intervention with inhaled corticosteroids can improve asthma control and normalize lung function. However, it remains to be determined whether intervention with inhaled corticosteroids or any other long-term-control therapy can prevent irreversible airway obstruction that may be associated with asthma (Evidence D).

Pathogenesis and Definition: Child Onset Asthma (page 10, column 1, paragraph 2 in EPR-2)

Asthma often begins in childhood, and when it does, it is frequently found in association with atopy, which is the genetic susceptibility to produce IgE directed toward common environmental allergens, including house-dust mites, animal proteins, and fungi (Larsen 1992). With the production of IgE antibodies, mast cells and possibly other airway cells (e.g., lymphocytes) are sensitized and become activated when they encounter specific antigens. Although atopy has been found in 30 to 50 percent of the general population, it is frequently found in the absence of asthma. Nevertheless, atopy is one of the strongest predisposing factors in the development of asthma (Sporik et al., 1990). Furthermore, a large epidemiologic study shows that among children who have recurrent episodes of wheezing during the first 3 years of life and have either one of two major risk factors (parental history of asthma or physician diagnosis of atopic dermatitis) or two of three minor risk factors (wheezing apart from colds, peripheral blood eosinophilia, or physician diagnosis of allergic rhinitis) have a 76 percent probability of developing asthma during the school years (Evidence C) (Castro-Rodriguez et al. 2000).

Pathogenesis and Definition. Airway Remodeling (page 11, column 2, paragraph 3 in EPR-2)

Airway remodeling. In some patients with asthma, airflow limitation may be persistent and nonresponsive to treatment. This nonresponsiveness may be caused by changes in the structure of airways. These changes include wall thickening, subepithelial fibrosis, goblet cell hypermetaplasia, myofibroblast hyperplasia, mucocyte hyperplasia and hypertrophy, vascular remodeling, and epithelial hypertrophy (Elias 1999). Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response. Although yet to be fully explored, the importance of airway remodeling as a possible cause of persistent airflow limitation and the possible role of chronic inflammation as a cause of remodeling suggest a rationale for early intervention with anti-inflammatory therapy. This must be confirmed with specific, controlled studies.

Component 1: Measures of Assessment and Monitoring. Spirometry (page 28, column 1 in EPR-2)

The Expert Panel recommends that spirometery tests be done (1) at the time of initial assessment; (2) after treatment is initiated and symptoms and PEF have stabilized, to document attainment of (near) "normal" airway function; and (3) at least every 1 to 2 years to assess the maintenance of airway function. These spirometry measures should be followed over the patient's lifetime to detect potential for decline and rate of decline of pulmonary function over time (Evidence D).

Component 3: Pharmacologic Therapy. Key Points: The Medications, Inhaled Corticosteroids (page 58 in EPR-2)

Increased understanding of inhaled corticosteroids notes that:

- Fa[illegible] wi[illegible]ed steroids likely w[illegible] ver[illegible]a management, but its effect o[illegible] irreversible airway injury rema[illegible] deter[illegible] (SRE-Evidence

Component 3: Pharmacologic Therapy. Special Considerations for Managing Asthma in Different Age Groups. Infants and Young Children, Diagnosis (page 95, column 1, paragraph 2 in EPR-2)

Among children 5 years of age and younger the most common cause of asthma symptoms is viral respiratory infection. At present, the relative contributions of airway inflammation, bronchial smooth muscle abnormalities, or other structural factors in producing wheeze with acute viral upper respiratory infections are unknown. There appear to be two general patterns of illness in infants and children who have wheezing with acute viral upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood.

No clear markers to predict the prognosis for an individual child exist. However, epidemiologic studies suggest that for children less than 3 years of age who have more than three episodes of wheezing in a year (that last more than 1 day and affect sleep), the following predictive index identifies the risk associated with persistent asthma after 6 years of age. If a child has either (a) a physician diagnosis of atopic dermatitis or a parental history of asthma OR (b) two of the following: physician-diagnosed allergic rhinitis, greater than 4 percent peripheral blood eosinophilia, or wheezing apart from colds, then the child has a high likelihood (76 percent probability) of developing persistent asthma (Evidence C) (Martinez 1995; Castro-Rodriguez 2000). It is conceivable that early recognition and treatment of these high-risk children could result in secondary prevention of persistent asthma, although this is not yet established by clinical trials.

Component 3: Pharmacologic Therapy, Special Considerations for Managing Asthma in Different Age Groups. Infants and Young Children, Treatment (page 95, column 2 in EPR-2)

In deciding when to initiate daily long-term-control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma vs. the possible adverse effects of medications given over prolonged periods. There is evidence that anti-inflammatory treatment can reduce morbidity from wheezing in early childhood (Connett et al. 1993). Long-term studies in children 5 to 12 years of age at the time of enrollment conclude that inhal[illegible] corticosteroids improve health outcomes for c[illegible]ith mild or moderate persistent asthma [illegible] the potential albeit small risk of delayed [illegible]th from the use of inhaled corticosteroids is we[illegible]ced by their effectiveness (SRE-Evidence A[illegible] 2000). Further, available long-term data [illegible] that [illegible]dren treated with inhaled [illegible]icost[illegible] achieve their predicted adult heights (Age[illegible]edersen 2000). It is noted that the [illegible] prosp[illegible] studies on growth involved [illegible]nide a[illegible]ne retrospective analyses [illegible]luded st[illegible]n bec[illegible]ethasone, but the results have be[illegible]rali[illegible]de all inhaled corticosteroi[illegible]ough different preparations and deli[illegible]ces ma[illegible]temic effect at different doses, all s[illegible] of numerous [illegible]eparations sugg[illegible]pot[illegible] effect of [illegible]nhaled corticost[illegible]on g[illegible] drug class eff[illegible] children[illegible]ie adverse effe[illegible]ated to inh[illegible]costeroid therapy, other o[illegible] (cromolyn, LTRA, nedocromil, or theop[illegible]e) for initiating or maintaining long-ter[illegible]ontrol therapy are available.

Based on high-quality evidence, the Expert Panel recommends long-term-control therapy for children with mild or moderate persistent asthma because it controls and prevents asthma symptoms (SRE Evidence A). However, evidence to date is insufficient to permit conclusions regarding whether early vs. delayed intervention with daily long-term-control medication will alter the underlying course of the disease. Although a preliminary study suggests that

appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a recent long-term RCT in children 5 to 12 years of [illegible] 2000) (SRE-Evidence A, B). The [illegible] does not support [illegible] in the [illegible] 5 to 12 years of age with [illegible] persistent asthma have a progressive [illegible] lung function that can be prevented by [illegible] term-control medication [illegible] data from other large group [illegible] the timing of the CAMP inte[illegible] was too late, as most loss of lung function in childhood asth[illegible] appears to occur in the first 3 to 5 years of [illegible] (Martinez et al. 1995). However, it has not been determined whether early recognition of children at high risk of developing persistent asthma [illegible] with early therapeutic intervention will either prevent the loss of lung function or prevent the development of persistent disease. Currently, critical prospective studies to address these issues are in progress. Similarly, to date no studies have evaluated whether intervention with inhaled corticosteroids can prevent the more rapid decline in lung function that can occur in adults with asthma.

Recommendations for Future Research

The SRE revealed methodological problems in most of the studies that evaluated the effect of inhaled corticosteroids on the progression of asthma. RCTs designed explicitly to address the research question are urgently needed. Further, new opportunities are now available to treat children younger than 5 years of age in whom the incidence of asthma onset is highest (Yuninger et al. 1992) and the risk for declines in lung function growth is high (Stern 2000; Castro-Rodriquez 2000). For example, LTRA is available for children as young as 2 years of age and inhaled corticosteroid nebulizing suspension for children as young as 1 year of age. In addition, new classes of medication that may be feasible for young children currently are being evaluated for their potential to modify disease: e.g., anti-IgE agents, cytokine antagonists, and cytokine receptor antagonists.

Because disease onset is high in children younger than 5 years of age and because these children are initially evaluated and managed by primary care physicians, it is important to establish firm diagnostic criteria for persistent asthma. Further, a refinement in the definition of disease progression must occur and methods to monitor progression should be designed and evaluated for use in clinical practice.

Specifically, more information in the following areas is needed to enhance our knowledge about the natural progression of asthma in children and adults, as well as appropriate interventions to alter it:

- Additional long-term studies, lasting a minimum of 2 years, of each medication class (e.g., inhaled corticosteroids, LTRAs, anti-IgE) in order to define the impact of treatment on the progression of asthma. Studies should:
  - In young children, be designed to assess for effect on measures including pulmonary function
  - In adults, be designed to examine whether loss of pulmonary function may be a unique feature of adult asthma, especially adult-onset asthma.
- Studies to determine the significance of declines in lung function and its relevance to other long-term events, including quality of life and severity of symptoms (acute exacerbations, symptoms, nighttime awakenings). Identification of the most appropriate pulmonary function measure to use for monitoring lung function growth in children and lung function declines in adults.
- Studies to identify the prevalence of airway remodeling and whether it can be predicted by asthma phenotype and genotype.
- Studies to identify methods for reliably and easily measuring and interpreting pulmonary function in young children. Forced oscillation could improve the feasibility of pulmonary function testing in young children, but these tests must be verified.
- Validation of a profile to predict persistent asthma and levels of asthma severity.

- Studies to identify and compare relevant outcomes that define disease progression and measure the effects of interventions to alter it. Pulmonary function, airway hyperresponsiveness, markers of inflammation, symptoms, medication use, and disease severity classifications are some outcomes of interest.

- Studies to design and evaluate methods for use in primary clinical practice to monitor individuals for progression of their disease. Serial measures of pulmonary function, assessments of medication requirements and urgent care visits over time, and, for infants, application of the asthma predictive index are possible approaches.

- Studies to evaluate when long-term-control therapy might be discontinued.

- Studies to evaluate the effectiveness of early use of environmental control measures, with or without pharmacologic therapy, alter the progression of disease.

Key Evidence Tables

Table 3-1. Study Characteristics

Citation	Study Design	Setting	Asthma Severity	Eligibility
Overbeek, Huib, Kerstjens et al. 1996	Open label extension of randomized parallel arm, double-blinded, placebo controlled trial	Country: Netherlands Funding: Pharmacologic + government grant Tx Setting: Unknown/Other; Multicenter	Stated: Not specified Estimated: Unable to estimate	Patient eligibility based on lung function only. (1) FEV_1 (type not specified) minimum 1.2 L and 1.64 to 4.5 residual SDs below predicted, or FEV_1/inspiratory vital capacity ratio >1.64 residual SDs below predicted. (2) Histamine PC20 maximum 8 mg/mL. Exclusions: Patients with medication use or conditions likely to interfere with the purpose of the study.
Haahtela, Jarvinen, Kava et al. 1994	Open label extension of randomized parallel arm, double-blinded, controlled trial	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other; Multicenter	Stated: Mild Estimated: Mild	Patient eligibility based on lung function and symptoms. FEV_1 (postdose) minimum 80% of predicted; increase of more than 15% after inhalation of $beta_2$-agonist or decrease of more than 15% after exercise tolerance test. Maximum duration of symptoms 12 months. Exclusions: History of smoking within 6 months, regular asthma treatment, prior treatment with corticosteroids or cromolyn.
Agertoft and Pedersen 1994	Prospective cohort analysis within parallel, controlled trial; patients stratified by prior duration of asthma	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other	Stated: Mild-moderate Estimated: Mild-Severe	Patient eligibility based on utilization and stated severity. Minimum of three prior visits to clinic within past year, with mild or moderate persistent asthma. Exclusions: Prior use of inhaled corticosteroids for more than 2 weeks per year; other chronic diseases.
Selroos, Pietinalho, Lofroos et al. 1995	Prospective cohort study; patients stratified by prior duration of asthma	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other	Stated: Mild-moderate Estimated: Mild-Severe	Patient eligibility based on lung function and symptoms. FEV_1 (type not specified) maximum 75% of predicted or PEF (a.m. clinic) maximum 75% of predicted; and/or use of inhaled bronchodilators >3x/week, and/or regular asthma symptoms during day or night, and/or reduced exercise tolerance. Exclusions: Prior use of inhaled corticosteroids; irreversible airway obstruction.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 3-2. Study Parameters

Citation	Pretreatment	Study Arm	Number Enrolled	Costicosteroid Delay	Treatment
Overbeek, Huib, Kerstjens et al. 1996	None	Inhaled corticosteroid—immediate		Corticosteroids delayed 0 months, then administered for 36 months	All patients received 200 mcg beclomethasone dipropionate 4x daily; all patients received 500 mcg terbutaline 4x daily.
		Inhaled corticosteroid—delayed		Corticosteroids delayed 30 months, then administered for 6 months	All patients received 500 mcg terbutaline 4x daily for entire study. Some patients received 40 mcg ipratropium bromide 4x daily for first 30 months of study. All patients received 200 mcg beclomethasone dipropionate 4x daily for final 6 months of study.
Haahtela, Jarvinen, Kava et al. 1994	Run-in 2 weeks to establish patient eligibility	Inhaled corticosteroid—immediate		Corticosteroids delayed 0 months, then administered for 36 months	All patients received 600 mcg budesonide 2x daily for first 24 months, then reduced to 200 mcg 2x daily for final 12 months of study.
		Inhaled corticosteroid—delayed		Corticosteroids delayed 24 months, then administered for 12 months	All patients received 600 mcg budesonide 2x daily for final 12 months of study.
Agertoft and Pedersen 1994	Run-in 52 weeks to establish patient eligibility	Inhaled corticosteroid—immediate		Prior duration of asthma 0–12 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
		Inhaled corticosteroid—delayed 1		Prior duration of asthma 12–24 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
		Inhaled corticosteroid—delayed 2		Prior duration of asthma 24–36 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
		Inhaled corticosteroid—delayed 3		Prior duration of asthma 12–24 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
Selroos, Pietinalho, Lofroos et al. 1995	None	Inhaled corticosteroid—immediate		Prior duration of asthma 0–6 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 1		Prior duration of asthma 6–12 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 2		Prior duration of asthma 12–24 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 3		Prior duration of asthma 24–60 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 4		Prior duration of asthma 60–120 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
		Inhaled corticosteroid—delayed 5		Prior duration of asthma >120 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Key Evidence Tables

Table 3-3. Lung Function Outcomes: FEV_1

Citation	Study	Number Enrolled	Number Evaluable	Study Duration (years)	
Overbeek, Huib, Kerstjens et al. 1996	Inhaled corticosteroid—immediate	91	49	3.0	
	Inhaled corticosteroid—delayed	183	53	3.0	
Haahtela, Jarvinen, Kava et al. 1994	Inhaled corticosteroid—immediate	50	16	3.0	
	Inhaled corticosteroid—delayed	53	36	3.0	
Agertoft and Pedersen 1994	Inhaled corticosteroid—immediate			3.7	
	Inhaled corticosteroid—delayed 1			3.7	
	Inhaled corticosteroid—delayed 2			3.7	
	Inhaled corticosteroid—delayed 3			3.7	
Selroos, Pietinalho, Lofroos et al. 1995	Inhaled corticosteroid—immediate	14		2.0	
	Inhaled corticosteroid—delayed 1	35		2.0	
	Inhaled corticosteroid—delayed 2	13		2.0	
	Inhaled corticosteroid—delayed 3	19		2.0	
	Inhaled corticosteroid—delayed 4	15		2.0	
	Inhaled corticosteroid—delayed 5	9		2.0	

	FEV_1 Baseline	FEV_1 Final	FEV_1 P-Value	Comments
	64.6 +/- 14.1% predicted	13.8% pred (change, 95% CI, 7.7–18.7)		Number of patients enrolled includes both COPD and asthma patients; number evaluable includes only asthma patients.
	61.2 +/- 15.6% predicted	8.5% pred (change, 95% CI, 3.3–15.9)	NS	Comparison only made of rise in FEV_1 during initial 3 months' treatment with inhaled corticosteroids in both groups.
	3.17 +/- 0.8 L	3.32 L		Values represent FEV_1 at start of initial study and final FEV_1 after 3 years.
	3.05 +/- 0.7 L	3.07 L		No statistical comparison performed on change in FEV_1 from start of study until final end-point.
	NR	8.2% pred/yr (change, 95% CI, 6.1, 10.3)		Final FEV_1 % predicted 101 +/- 13.6% Calculation of % increase/yr in FEV_1 by linear regression probably not appropriate.
	NR	6.7% pred/yr (change, 95% CI, 5.0, 8.4)		
	NR	3% pred/yr (change, 95% CI, 1.8, 4.2)		
	NR	2.4% pred/yr (95% CI, 1.1, 3.7)		Final FEV_1 % predicted 96.2 +/- 9.5%, $p < 0.05$ as compared to inhaled corticosteroid-immediate group.
	70 +/- 21% predicted	87 +/- 18.7% predicted		
	70 +/- 21% predicted	75 +/- 17.7% predicted .	0.100	Comparison of change in FEV_1 vs. Ctl
	78 +/- 18% predicted	85 +/- 18.0% predicted	<.0500	Comparison of change in FEV_1 vs. Ctl
	60 +/- 16% predicted	68 +/- 21.8% predicted	NS	Comparison of change in FEV_1 vs. Ctl
	62 +/- 18% predicted	66 +/- 19.4% predicted	<.0500	Comparison of change in FEV_1 vs. Ctl
	67 +/- 30.0% predicted	67 +/- 30.0% predicted	<.0100	Comparison of change in FEV_1 vs. Ctl

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Expert Panel Report
Guidelines for the
Diagnosis and
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Asthma
Appendix A:
Updated Charts for the
Management of Asthma
for Reference
ASTHMA

Appendix A–1. STEPWISE APPROACH FOR MANAGING ASTHMA

Figure 1. Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) With Acute or Chronic Asthma (Updates EPR-2 Figures 3–4a and 3–6)

Classify Severity: Clinical Features Before Treatment or Adequate Control	Symptoms	Medications Required To Maintain Long-Term Control: Daily Medications
Step 4 Severe Persistent	Continual / Frequent	■ Preferred treatment: – High-dose inhaled corticosteroids AND – Long-acting inhaled $beta_2$-agonists AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily / >1 night/week	■ Preferred treatments: – Low-dose inhaled corticosteroids and long-acting inhaled $beta_2$-agonists OR – Medium-dose inhaled corticosteroids. ■ Alternative treatment: – Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline. If needed (particularly in patients with recurring severe exacerbations): ■ Preferred treatment: – Medium-dose inhaled corticosteroids and long-acting $beta_2$-agonists. ■ Alternative treatment: Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.
Step 2 Mild Persistent	>2/week but <1x/day / >2 nights/month	■ Preferred treatment: – Low-dose inhaled corticosteroids (with nebulizer or MDI with holding chamber with or without face mask or DPI). ■ Alternative treatment (listed alphabetically): – Cromolyn (nebulizer is preferred or MDI with holding chamber) OR leukotriene receptor antagonist.
Step 1 Mild Intermittent	≤2 days/week / ≤2 nights/month	■ No daily medication needed.

Quick Relief — All Patients

- Bronchodilator as needed for symptoms. Intensity of treatment will depend upon severity of exacerbation.
  - Preferred treatment: Short-acting inhaled $beta_2$-agonists by nebulizer or face mask and spacer/holding chamber
  - Alternative treatment: Oral $beta_2$-agonists
- With viral respiratory infection
  - Bronchodilator q 4–6 hours up to 24 hours (longer with physician consult); in general, repeat no more than once every 6 weeks
  - Consider systemic corticosteroid if exacerbation is severe or patient has history of previous severe exacerbations
- Use of short-acting $beta_2$-agonists >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.

Step down
Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.

Step up
If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/parent's work missed
- Minimal use of short-acting inhaled $beta_2$-agonist
- Minimal or no adverse effects from medications

Note

- The stepwise approach is intended to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs.
- There are very few studies on asthma therapy for infants.
- Gain control as quickly as possible (a course of short systemic corticosteroids may be required); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled $beta_2$-agonists. Overreliance on short-acting inhaled $beta_2$-agonists (e.g., use of short-acting inhaled $beta_2$-agonist every day, increasing use or lack of expected effect, or use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy.
- Provide parent education on asthma management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Consultation with an asthma specialist is recommended for patients with moderate or severe persistent asthma. Consider consultation for patients with mild persistent asthma.

APPENDIX A–1. STEPWISE APPROACH FOR MANAGING ASTHMA (continued)

Figure 2. Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age: Treatment (Updates EPR-2 Figures 3–4a and 3–4b)

Classify Severity: Clinical Features Before Treatment or Adequate Control			Medications Required To Maintain Long-Term Control
	Symptoms/Day Symptom	PEF or FEV_1 PEF Variability	Daily Medications
Step 4 Severe Persistent	Continual Frequent	≤60% >30%	■ Preferred treatment: – High-dose inhaled corticosteroids AND – Long-acting inhaled $beta_2$-agonists AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily >1 night/week	>60% – <80% >30%	■ Preferred treatment: – Low-to-medium dose inhaled corticosteroids and long-acting inhaled $beta_2$-agonists. ■ Alternative treatment (listed alphabetically): – Increase inhaled corticosteroids within medium-dose range OR – Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. If needed (particularly in patients with recurring severe exacerbations): ■ Preferred treatment: – Increase inhaled corticosteroids within medium-dose range and add long-acting inhaled $beta_2$-agonists. ■ Alternative treatment: – Increase inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline.
Step 2 Mild Persistent	>2/week but < 1x/day >2 nights/month	≥80% 20–30%	■ Preferred treatment: – Low-dose inhaled corticosteroids. ■ Alternative treatment (listed alphabetically): cromolyn, leukotriene modifier, nedocromil, OR sustained release theophylline to serum concentration of 5–15 mcg/mL.
Step 1 Mild Intermittent	≤2 days/week ≤2 nights/month	≥80% <20%	■ No daily medication needed. ■ Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.

Quick Relief
All Patients

- Short-acting bronchodilator: 2–4 puffs short-acting inhaled $beta_2$-agonists as needed for symptoms.
- Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroids may be needed.
- Use of short-acting $beta_2$-agonists >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.

Step down
Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.

Step up
If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled $beta_2$-agonist
- Minimal or no adverse effects from medications

Note

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is % of personal best; FEV_1 is % predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroids); then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled $beta_2$-agonists. Overreliance on short-acting inhaled $beta_2$-agonists (e.g., use of short-acting inhaled $beta_2$-agonist every day, increasing use or lack of expected effect, or use of approximately one canister a month even if not using it every day) indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy.
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if step 4 care is required. Referral may be considered if step 3 care is required.

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS

Figure 1. Usual Dosages for Long-Term-Control Medications (Updates EPR-2 Figure 3–5a)

Medication	Dosage Form	Adult Dose	Child Dose*	Comments
Inhaled Corticosteroids *(See Estimated Comparative Daily Dosages for Inhaled Corticosteroids.)*				
Systemic Corticosteroids			*(Applies to all three corticosteroids)*	
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	7.5–60 mg daily in a single dose in a.m. or qod as needed for control	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control	■ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). If daily doses are required, one study suggests improved efficiency and no increase in adrenal suppression when administered at 3 p.m. (Beam et al. 1992).
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	Short-course "burst": to achieve control 40–60 mg per day as single or 2 divided doses for 3–10 days	Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration.
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc			■ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Long-Acting Inhaled Beta$_2$-Agonists				■ Should not be used for symptom relief or exacerbations. Use with corticosteroids.
Salmeterol	MDI 21 mcg/puff	2 puffs q 12 hours	1–2 puffs q 12 hours	■ May use one dose nightly for symptoms.
	DPI 50 mcg/blister	1 blister q 12 hours	1 blister q 12 hours	
Formoterol	DPI 12 mcg/single-use capsule	1 capsule q 12 hours	1 capsule q 12 hours	■ Efficacy and safety have not been studied in children <5 years of age.
				■ Each capsule is for single use only; additional doses should not be administered for at least 12 hours.
				■ Capsules should be used only with the Aerolizor™ inhaler and should not be taken orally.

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 1. Usual Dosages for Long-Term-Control Medications (Updates EPR-2 Figure 3–5a)

Medication	Dosage Form	Adult Dose	Child Dose*	Comments
Combined Medication				
Fluticasone/Salmeterol	DPI 100 mcg, 250 mcg, or 500 mcg/ 50 mcg	1 inhalation bid; dose depends on severity of asthma	1 inhalation bid; dose depends on severity of asthma	■ Not FDA approved in children <12 years of age. 100/50 for patient not controlled on low-to-medium dose inhaled corticosteroids. 250/50 for patients not controlled on medium-to-high dose inhaled corticosteroids.
Cromolyn and Nedocromil				
Cromolyn	MDI 1 mg/puff Nebulizer 20 mg/ampule	2–4 puffs tid-qid 1 ampule tid-qid	1–2 puffs tid-qid 1 ampule tid-qid	■ One dose prior to exercise or allergen exposure provides effective prophylaxis for 1–2 hours.
Nedocromil	MDL 1.75 mg/puff	2–4 puffs bid-qid	1–2 puffs bid-qid	■ See cromolyn above.
Leukotriene Modifiers				
Montelukast	4 mg or 5 mg chewable tablet 10 mg tablet	10 mg qhs	■ 4 mg qhs (2–5 years of age) 5 mg qhs (6–14 years of age) 10 mg qhs (>14 years of age)	■ Montelukast exhibits a flat dose-response curve. Doses >10 mg will not produce a greater response in adults.
Zafirlukast	10 or 20 mg tablet	40 mg daily (20 mg tablet bid)	■ 20 mg daily (7–11 years of age) (10 mg tablet bid)	■ For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.
Zileuton	300 or 600 mg tablet	2,400 mg daily (give tablets qid)		■ For zileuton, monitor hepatic enzymes (ALT).
Methylxanthines				
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day	Starting dose 10 mg/kg/day; usual max: ■ <1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥1 year of age: 16 mg/kg/day	■ Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage). ■ Due to wide inter-patient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important. ■ See figure 3–5a, page 87, EPR-2 for factors that can affect theophylline levels.

*Children ≤ 12 years of age

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 2. Estimated Comparative Daily Dosages for Inhaled Corticosteroids (Updates EPR-2 Figure 3–5b)

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Adult	Child*	Adult	Child*	Adult	Child*
Beclomethasone CFC 42 or 84 mcg/puff	168–504 mcg	84–336 mcg	504–840 mcg	336–672 mcg	> 840 mcg	> 672 mcg
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	80–160 mcg	240–480 mcg	160–320 mcg	> 480 mcg	> 320 mcg
Budesonide DPI 200 mcg/inhalation	200–600 mcg	200–400 mcg	600–1,200 mcg	400–800 mcg	> 1,200 mcg	> 800 mcg
Inhalation suspension for nebulization (child dose)		0.5 mg		1.0 mg		2.0 mg
Flunisolide 250 mcg/puff	500–1,000 mcg	500–750 mcg	1,000–2,000 mcg	1,000–1,250 mcg	> 2,000 mcg	> 1,250 mcg
Fluticasone MDI: 44, 110, or 220 mcg/puff	88–264 mcg	88–176 mcg	264–660 mcg	176–440 mcg	> 660 mcg	> 440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100–300 mcg	100–200 mcg	300–600 mcg	200–400 mcg	> 600 mcg	> 400 mcg
Triamcinolone acetonide 100 mcg/puff	400–1,000 mcg	400–800 mcg	1,000–2,000 mcg	800–1,200 mcg	> 2,000 mcg	> 1,200 mcg

* Children ≤12 years of age

Note

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effect.
- Comparative dosages in the EPR-2 were based on a limited number of published comparative clinical trials and extrapolation of differences in topical potency and lung delivery. This updated comparative dosage chart is based on review of recently published clinical trials involving more than 5,000 patients and published reviews (Barnes PJ et al. 1998; Kelly 1998; Pedersen 1997). The key differences from the EPR-2 include a higher dosage of budesonide and recommendations for two newly available medications: beclomethasone HFA and budesonide suspension for nebulization. The rationale for these changes is summarized as follows:
  - The high dose is the dose that appears likely to be the threshold beyond which significant hypothalamic-pituitary-adrenal (HPA) axis suppression is produced, and, by extrapolation, the risk is increased for other clinically significant systemic effects if used for prolonged periods of time (Martin et al. 2002; Szefler et al. 2002).
  - The low and medium dose reflects findings from dose-ranging studies in which incremental efficacy within the low-to-medium dose ranges was established without increased systemic effect as measured by overnight cortisol excretion. The studies demonstrated a relatively flat dose-response curve for efficacy at the medium-dose range; that is, increasing the dose to high-dose range did not significantly increase efficacy but did increase systemic effect (Martin et al. 2002; Szefler et al. 2002).
  - The dose for budesonide dry powder inhaler (DPI) is based on recently available comparative data with other medications, rather than the comparison to budesonide metered-dose inhaler (MDI) that was used in the EPR-2. These new data, including a meta-analysis of seven studies, show that budesonide DPI is comparable to approximately one-half the microgram dose of fluticasone (Barnes NC et al. 1998; Nielsen and Dahl 2000).
  - The dose for beclomethasone HFA is one-half the dose for beclomethasone CFC, based on studies demonstrating that the different pharmaceutical properties of the medications result in enhanced lung delivery for the HFA (a less forceful spray from the HFA propellant and a reengineered nozzle that allows a smaller particle size) (Leach et al. 1998; Busse et al. 1999; Gross et al. 1999; Thompson et al. 1998).
  - The dose for budesonide nebulizer suspension is based on efficacy and safety studies (Baker et al. 1999; Kemp et al. 1999; Shapiro et al. 1998), but no comparative studies with other inhaled corticosteroids are available. It is noted that the efficacy studies did not demonstrate a clear or consistent dose-response, although the high dose of 2.0 mg was effective in a placebo-controlled study in 40 infants with severe asthma (de Blic et al. 1996). In a small open-label long-term safety study, the ACTH stimulated cortisols appeared lower in the 13 infants receiving the high dose of 2.0 mg budesonide compared to infants receiving lower doses, but this was not statistically significant due, perhaps, to the small study size (Scott and Skoner 1999).
- Some doses may be outside package labeling, especially in the high-dose range.
- MDI dosages are expressed as the actuater dose (the amount of the drug leaving the actuater and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, not all of which is available to the patient), which is used in many European countries and in some scientific literature. DPI doses are expressed as the amount of drug in the inhaler following activation.

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 3. Usual Dosages for Quick-Relief Medications (Updates EPR-2 Figure 3–5d)

Medication	Dosage Form	Adult Dose	Child Dose*	Comments
Short-Acting Inhaled $Beta_2$-Agonists				
	MDI			
Albuterol	90 mcg/puff, 200 puffs	▪ 2 puffs 5 minutes prior to exercise ▪ 2 puffs tid-qid prn	▪ 1–2 puffs 5 minutes prior to exercise ▪ 2 puffs tid-qid prn	▪ An increasing use or lack of expected effect indicates diminished control of asthma. ▪ Not generally recommended for long-term treatment. Regular use on a daily basis indicates the need for additional long-term-control therapy. ▪ Differences in potency exist, but all products are essentially comparable on a per puff basis. ▪ May double usual dose for mild exacerbations. ▪ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.
Albuterol HFA	90 mcg/puff, 200 puffs			
Pirbuterol	200 mcg/puff, 400 puffs			
	DPI			
Albuterol Rotahaler	200 mcg/capsule	1–2 capsules q 4–6 hours as needed and prior to exercise	1 capsule q 4–6 hours as needed and prior to exercise	
	Nebulizer solution			
Albuterol	5 mg/mL (0.5%) 2.5 mg/3 mL 1.25 mg/3 mL 0.63 mg/3 mL	1.25–5 mg in 3 cc of saline q 4–8 hours	0.05 mg/kg (min 1.25 mg, max 2.5 mg) in 3 cc of saline q 4–6 hours	▪ May mix with cromolyn or ipratropium nebulizer solutions. May double dose for severe exacerbations.
	Nebulizer solution			
Bitolterol	2 mg/mL (0.2%)	0.5–3.5 mg (0.25–1 cc) in 2–3 cc of saline q 4–8 hours	Not established	▪ May not mix with other nebulizer solutions.
	Nebulizer solution			
Levalbuterol (R-albuterol)	0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/3 mL	0.63 mg–2.5 mg q 4–8 hours	0.025 mg/kg (min. 0.63 mg, max. 1.25 mg) q 4–8 hours	▪ 0.63 mg of levalbuterol is equivalent in efficacy and side effects to 1.25 mg of racemic albuterol. The product is a sterile-filled preservative-free unit dose vial.

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 3. Usual Dosages for Quick-Relief Medications (Updates EPR-2 Figure 3–5d)

Medication	Dosage Form	Adult Dose	Child Dose*	Comments
Anticholinergics				
Ipratropium	*MDI* 18 mcg/puff, 200 puffs	2–3 puffs q 6 hours	1–2 puffs q 6 hours	▪ Evidence is lacking for anticholinergics producing added benefit to beta$_2$-agonists in long-term-control asthma therapy.
	Nebulizer solution 0.25 mg/mL (0.025%)	0.25 mg q 6 hours	0.25–0.5 mg q 6 hours	
Ipratropium with albuterol	*MDI* 18 mcg/puff of ipratropium bromide and 90 mcg/puff of albuterol. 200 puffs/canister	2–3 puffs q 6 hours	1–2 puffs q 8 hours	
	Nebulizer solution 0.5 mg/3 mL ipratropium bromide and 2.5 mg/3 mL albuterol	3 mL q 4–6 hours	1.5–3 mL q 8 hours	▪ Contains EDTA to prevent discoloration of the solution. This additive does not induce bronchospasm.
Systemic Corticosteroids			the three corticosteroids)	
Methylprednisolone	2, 4, 6, 8, 16, 32 mg tablets	▪ Short course "burst": 40–60 mg/day as single or 2 divided doses for 3–10 days	▪ Short course "burst" 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days	▪ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ▪ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc			
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc			
(Methylprednisolone acetate)	*Repository injection* 40 mg/mL 80 mg/mL	240 mg IM once	7.5 mg/kg IM once	▪ May be used in place of a short burst of oral steroids in patients who are vomiting or if adherence is a problem.

* Children ≤12 years of age

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS

Figure 4. Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital (Updates EPR-2 Figure 3–10)

Medication	Dosages		
	Adult Dose	Child Dose*	Comments
Short-Acting Inhaled $Beta_2$-Agonists			
Albuterol			
Nebulizer solution (5.0 mg/mL, 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization	Only selective $beta_2$-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min.
MDI (90 mcg/puff)	4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed	4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver. Use spacer/holding chamber	As effective as nebulized therapy if patient is able to coordinate.
Bitolterol			
Nebulizer solution (2 mg/mL)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a mg basis	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI (370 mcg/puff)	See albuterol dose	See albuterol dose	Has not been studied in severe asthma exacerbations.
Levalbuterol (R-albuterol)			
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL)	1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed, or 5–7.5 mg/hour continuously	0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed, or 0.25 mg/kg/hour by continuous nebulization	0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects.
Pirbuterol			
MDI (200 mcg/puff)	See albuterol dose	See albuterol dose; thought to be half as potent as albuterol on a mg basis	Has not been studied in severe asthma exacerbations.
Systemic (Injected) $Beta_2$-Agonists			
Epinephrine 1:1000 (1 mg/mL)	0.3–0.5 mg every 20 minutes for 3 doses sq	0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for 3 doses sq	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/mL)	0.25 mg every 20 minutes for 3 doses sq	0.01 mg/kg every 20 minutes for 3 doses then every 2–6 hours as needed sq	No proven advantage of systemic therapy over aerosol.

APPENDIX A–2. USUAL DOSAGES FOR ASTHMA MEDICATIONS (continued)

Figure 4. Dosages of Drugs for Asthma Exacerbations in Emergency Medical Care or Hospital (Updates EPR-2 Figure 3–10)

Medication	Dosages		
	Adult Dose	Child Dose*	Comments
Anticholinergics			
Ipratropium bromide			
Nebulizer solution (0.25 mg/mL)	0.5 mg every 30 minutes for 3 doses, then every 2–4 hours as needed	0.25 mg every 20 minutes for 3 doses, then every 2 to 4 hours	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to beta$_2$-agonist therapy.
MDI (18 mcg/puff)	4–8 puffs as needed	4–8 puffs as needed	Dose delivered from MDI is low and has not been studied in asthma exacerbations.
Ipratropium with albuterol			
Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol.)	3 mL every 30 minutes for 3 doses, then every 2–4 hours as needed	1.5 mL every 20 minutes for 3 doses, then every 2–4 hours	Contains EDTA to prevent discoloration. This additive does not induce bronchospasm.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg of albuterol.)	4–8 puffs as needed	4–8 puffs as needed	
Systemic Corticosteroids			
	Dosages and comments apply to all three corticosteroids)		
Prednisone Methylprednisolone Prednisolone	120–180 mg/day in 3 or 4 divided doses for 48 hours, then 60–80 mg/day until PEF reaches 70% of predicted or personal best	1 mg/kg every 6 hours for 48 hours then 1–2 mg/kg/day (maximum = 60 mg/day) in 2 divided doses until PEF 70% of predicted or personal best	For outpatient "burst" use 40–60 mg in single or 2 divided doses for adults (children: 1–2 mg/kg/day, maximum 60 mg/day) for 3–10 days.

* Children ≤12 years of age

Note

No advantage has been found for higher dose corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy provided gastrointestinal transit time or absorption is not impaired. The usual regimen is to continue the frequent multiple daily dose until the patient achieves an FEV_1 or PEF of 50 percent of predicted or personal best and then lower the dose to twice daily. This usually occurs within 48 hours. Therapy following a hospitalization or emergency department visit may last from 3 to 10 days. If patients are then started on inhaled corticosteroids, studies indicate there is no need to taper the systemic corticosteroid dose. If the followup systemic corticosteroid therapy is to be given once daily, one study indicates that it may be more clinically effective to give the dose in the afternoon at 3 p.m., with no increase in adrenal suppression (Beam et al. 1992).

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Appendix B: Acronyms and Abbreviations

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ACTH	adrenocorticotropic hormone
AHRQ	Agency for Healthcare Research and Quality
BDP	beclomethasone dipropionate
BMD	bone mineral density
BUD	budesonide
CAMP	Childhood Asthma Management Program
CI	confidence interval
COPD	chronic obstructive pulmonary disease
ctl	control arm
DPI	dry powder inhaler
EIB	exercise-induced bronchospasm
EPR—Update2002	
EPR-2	Expert Panel Report-2
FDA	Federal Drug Administration
FEV_1	forced expiratory volume in 1 second
FP	fluticasone propionate
HPA	hypothalamic-pituitary-adrenal
IFN	interferon
IL	interleukin
kg	kilogram
LTRA	leukotriene receptor antagonist
MDI	metered-dose inhaler
MeSH	Medical Subject Heading
mg	milligram
mL	milliliter
NA	not available
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
NR	not reported
PEF	peak expiratory flow
pharm. ind.	pharmaceutical industry
Pred	predicted
RCT	randomized controlled trial
SD	standard deviation
SRE	systematic review of the evidence
sx	symptoms
TEC	Technology Evaluation Center
Th	T-helper
tx	treatment

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NHLBI Health Information Center
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